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WHAT'S NEW IN INTENSIVE CARE

Carbon dioxide pathophysiology and targets following acute brain injury

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Maintaining adequate cerebral oxygen delivery is fundamental to preventing secondary ischemic injury in patients with acute brain injuries (ABI). Regulation of arterial carbon dioxide tension ($PaCO_2$) plays a key role in this process, as $PaCO_2$ is a potent modulator of cerebral blood flow (CBF). In the absence of elevated intracranial pressure (ICP), targeting $PaCO_2$ within an appropriate clinical range can promote adequate cerebral oxygen delivery and minimize ischemic injury. This brief editorial outlines the physiologic relationship between $PaCO_2$ and CBF and summarizes evidence-based $PaCO_2$ management strategies across common ABI conditions (Fig. 1).

CO_2 and cerebral physiology

The relationship between $PaCO_2$ and CBF is nearly linear over a $PaCO_2$ range of 20–80 mmHg. Each 1 mmHg increase in $PaCO_2$ leads to an increase in CBF of approximately 3–6%, whereas each 1 mmHg decrease leads to a reduction in CBF by 1–3% (Fig. 1A) [1]. The degree to which $PaCO_2$ modulates CBF—termed CO_2 reactivity—can be diminished in older individuals or in the context of severe ABI [2]. Moreover, effects are regionally heterogeneous, with grey matter demonstrating two- to three-fold greater CO_2 reactivity than white matter [3].

The CBF response to CO_2 is mediated by changes in cerebrospinal fluid pH. CO_2 has a more potent and immediate effect on CBF than systemic arterial pH because it readily crosses the blood–brain barrier and directly alters perivascular pH. Hypercapnia leads to acidification of the cerebrospinal fluid and vasodilatation of pial resistance arterioles, increasing CBF and blood volume, and potentially increasing ICP in patients with limited compensatory reserve (Fig. 1B). Conversely, hypocapnia causes cerebrospinal fluid alkalosis, vasoconstriction of the pial arterioles, and reduced CBF [1]. The attendant reduction in blood volume reduces ICP and explains the clinical use of hyperventilation to control elevated ICP.

However, sustained and profound hyperventilation can lead to cerebral ischemia by reducing CBF. $PaCO_2$ levels of 25 mmHg within the first 24–36 h after ABI substantially increase metabolic stress markers in the cerebrospinal fluid (e.g., glutamate and lactate) [4], and imaging studies have demonstrated significant attenuation in CBF when $PaCO_2$ is lowered from 36 to 29 mmHg [5]. Profound hyperventilation is not recommended except briefly for refractory intracranial hypertension or imminent herniation [6, 7]. Despite lack of robust data, risks may be less pronounced with mild hypocapnia ($PaCO_2$ 32–35 mmHg) [8], supporting brief and cautious hyperventilation when elevated ICP is of concern.

CO_2 targets in ABI

General recommendations

Clinical guidelines recommend maintaining $PaCO_2$ within 35–45 mmHg in ABI patients without elevated ICP, with permissible reductions in patients with ICP elevation [6, 9]. A sub-analysis of the ENIO observational study (1476 patients) found a U-shaped association between $PaCO_2$ and outcomes, with marked increased in-hospital mortality at $PaCO_2 < 32$ mmHg and > 45 mmHg compared to normocapnia (35–45 mmHg). The highest mortality was seen with $PaCO_2 < 26$ mmHg [10].

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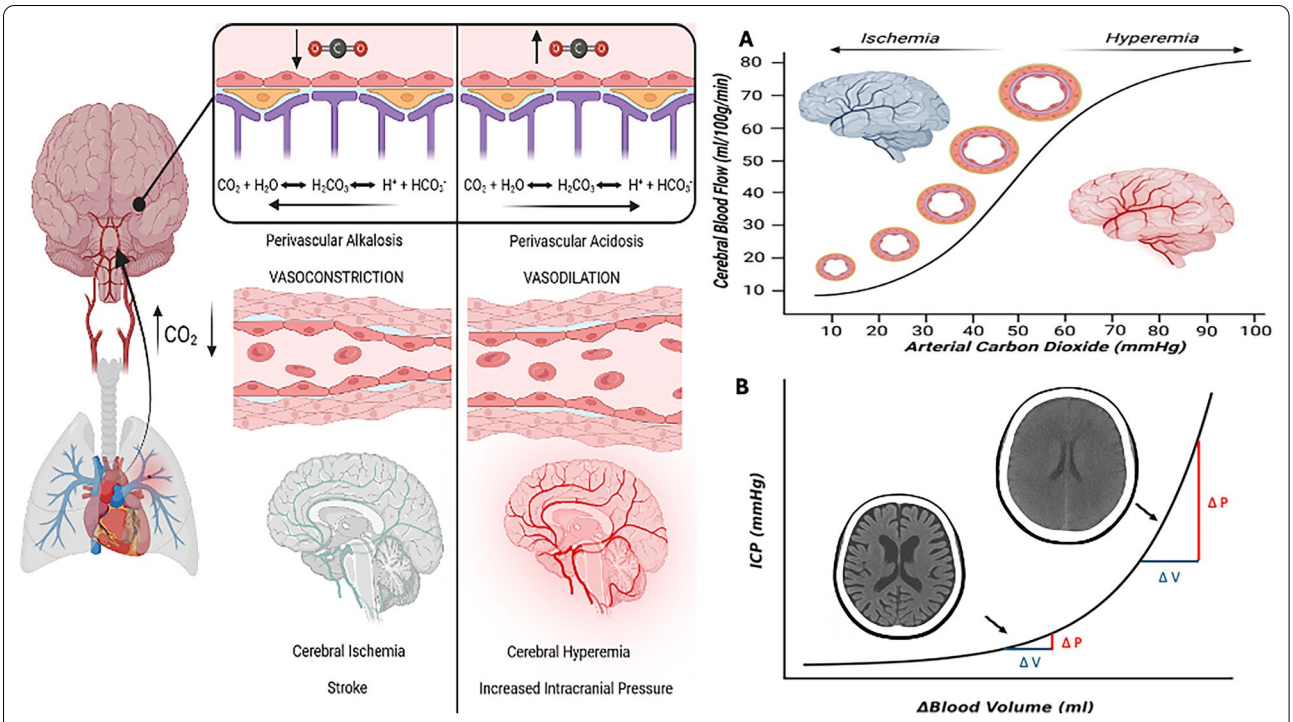

Fig. 1 Effect of carbon dioxide on CBF and ICP. The risks related to vasoconstriction and vasodilation and general pathophysiology of carbon dioxide and brain cerebral reactivity are explained. **A** The relationship between $PaCO_2$ and CBF is approximately linear between a $PaCO_2$ range of 20–80 mmHg. Within this range, $PaCO_2$ increases lead to perivascular acidosis, cerebral arteriolar vasodilatation, and an increase in CBF, whereas $PaCO_2$ decreases cause perivascular alkalosis, cerebral arteriolar vasoconstriction, and a decrease in CBF. The clinical implication of this relationship is that cerebral ischemia may occur at progressively lower $PaCO_2$ levels and hyperemia (with potential ICP elevation) may occur at progressively higher levels. **B** The relationship between changes in cerebral blood volume and ICP depend on baseline cerebral elastance. In patients with low cerebral elastance, for a given increase in $PaCO_2$, the corresponding increase in blood volume may lead to a small and clinically insignificant increase in ICP. On the other hand, in patients with increased cerebral elastance, the same increase in $PaCO_2$ and blood volume may lead to a much larger and potentially dangerous rise in ICP. *CBF* cerebral blood flow, *ICP* intracranial pressure, *$PaCO_2$* partial pressure of arterial carbon dioxide

Traumatic brain injury

The Seattle International Brain Injury Consensus Consortium suggests a tier-based approach to targeting $PaCO_2$ when managing ICP in patients with severe traumatic brain injury (tier 1, low-normal $PaCO_2$: 35–38 mmHg; tier 2, mild hypocapnia: 32–35 mmHg) [6]. The Brain Trauma Foundation guidelines advise against routinely lowering $PaCO_2$ below 30 mmHg [7], based partly on a randomized trial of 113 patients published over 30 years ago, where prolonged prophylactic hyperventilation ($PaCO_2$ 25 ± 2 mmHg) led to worse long-term outcomes compared to normocapnia ($PaCO_2$ 35 ± 2 mmHg) [11]. Notwithstanding, mean $PaCO_2$ varies substantially across hospitals [12]. Where available, brain oxygen monitoring (e.g., jugular venous oximetry or brain tissue probe) is recommended to guide the depth and duration of therapeutic hyperventilation, based on concern for CBF attenuation and subsequent hypoxia [6]. In the ongoing BONANZA and BOOST-III trials (ACTRN12619001328167 and NCT03754114), mild hypercapnia (45–50 mmHg) is part of a protocolized strategy to improve low brain tissue oxygen (via increasing CBF) when ICP is normal. This approach currently remains investigational and cannot be recommended in the absence of invasive intracranial monitors.

Ischemic and hemorrhagic stroke

$PaCO_2$ targets are not addressed in contemporary guidelines of patients with ischemic or hemorrhagic stroke, and general principles are often extrapolated from the traumatic brain injury literature [13]. Mechanical

ventilation guidelines in ABI recommend $PaCO_2$ targets of 35–45 mmHg [9], including in patients with stroke, but several disease-specific factors merit consideration.

Following ischemic stroke, CBF in the penumbra is often attenuated. In animal models, hyperventilation may induce a "steal" phenomenon that diverts blood into the penumbra from adjacent brain tissue [14]. However, this approach is not routinely recommended, and prolonged hyperventilation carries the risk of expanding ischemic regions, outweighing any potential benefit.

In patients with subarachnoid hemorrhage, spontaneous hyperventilation and hypocapnia are common. Hypocapnia-mediated attenuation of CBF is a concern, especially in patients with angiographic vasospasm or delayed cerebral ischemia, but "normalizing" $PaCO_2$ may also not be advisable for all patients due to risks related to sedation, paralysis, and loss of the neurologic examination. An individualized approach is often necessary. On the other hand, controlled hypercapnia (up to 60 mmHg) was shown to improve CBF and brain oxygenation without increasing ICP in a study of 6 patients with high-grade subarachnoid hemorrhage [15]. A subgroup analysis of the ENIO sub-study found that even mild hypocapnia was independently associated with in-hospital mortality following SAH, whereas hypercapnia was not [10]. Controlled hypercapnia could therefore represent an attractive therapeutic option for managing delayed cerebral ischemia in select patients, but further studies are needed.

In patients with intracranial hemorrhage, $PaCO_2$ management follows general recommendations as previously described. Avoiding hypercapnia is particularly important for patients with large hematomas causing mass effect, as even minor increases in CBF and blood volume can raise ICP in the setting of poor intracranial compliance (Fig. 1B).

Post-cardiac arrest brain injury

Current guidelines in this population recommend adjusting ventilation targets to maintain $PaCO_2$ within 35–45 mmHg [16]. In the TAME trial of 1700 patients with out-of-hospital cardiac arrest, targeting $PaCO_2$ of 50–55 mmHg did not improve neurologic function or reduce death at 6 months compared to normocapnia (35–45 mmHg) [17]. This neutral result may be explained by impaired CO_2 reactivity seen in many patients with post-cardiac arrest brain injury [2].

After return of spontaneous circulation, CBF typically has a transient hyperemic phase (10–30 min), followed by a more prolonged low-flow phase. Risks of hypocapnia-related ischemia are especially pronounced in the low-flow phase, highlighting the importance of strict avoidance of $PaCO_2 < 35$ mmHg after circulation is restored.

Conclusion

Normocapnia is advised for most patients with ABI, particularly in the acute phase when $PaCO_2$-mediated changes in CBF can significantly impact ICP and risk of secondary brain injury. Achieving mild hypocapnia ($PaCO_2$ 32–35 mmHg) with hyperventilation can be a valuable tool to manage raised ICP and acute ICP crises but should be used sparingly to avoid ischemic complications. Meanwhile, controlled hypercapnia remains an area of ongoing research. Future studies should explore personalized $PaCO_2$ management strategies.

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Declarations

Conflicts of interest

CR reports fees as speaker from BD. The other authors have no COI.

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References

1. Smith AL, Neufeld GR, Ominsky AJ, Wollman H (1971) Effect of arterial CO 2 tension on cerebral blood flow, mean transit time, and vascular volume. J Appl Physiol 31:701–707
2. Hoiland RL, Robba C, Menon DK, Citerio G, Sandroni C, Sekhon MS (2023) Clinical targeting of the cerebral oxygen cascade to improve brain oxygenation in patients with hypoxic-ischaemic brain injury after cardiac arrest. Intensive Care Med 49:1062–1078
3. Willie CK, Tzeng YC, Fisher JA, Ainslie PN (2014) Integrative regulation of human brain blood flow. J Physiol 592:841–859
4. Marion DW, Puccio A, Wisniewski SR, Kochanek P, Dixon CE, Bullian L, Carlier P (2002) Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury. Crit Care Med 30:2619–2625
5. Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, Downey SP, Williams G, Chatfield D, Matthews JC, Gupta AK, Carpenter TA, Clark JC, Pickard JD, Menon DK (2002) Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med 30:1950–1959
6. Hawryluk GWJ, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, Arrastia RD, Diringer M, Figaji A, Gao G, Geocadin R, Ghajar J, Harris O, Hoffer A, Hutchinson P, Joseph M, Kitagawa R, Manley G, Mayer S, Menon DK,

Meyfroidt G, Michael DB, Oddo M, Okonkwo D, Patel M, Robertson C, Rosenfeld JV, Rubiano AM, Sahuquillo J, Servadei F, Shutter L, Stein D, Stocchetti N, Taccone FS, Timmons S, Tsai E, Ullman JS, Vespa P, Videtta W, Wright DW, Zammit C, Chesnut RM (2019) A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med 45:1783–1794

7. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J (2017) Guidelines for the management of severe traumatic brain injury, Fourth Edition. Neurosurgery 80:6–15
8. Brandi G, Stocchetti N, Pagnamenta A, Stretti F, Steiger P, Klinzing S (2019) Cerebral metabolism is not affected by moderate hyperventilation in patients with traumatic brain injury. Crit Care 23:45
9. Robba C, Poole D, McNett M, Asehnoune K, Bösel J, Bruder N, Chieregato A, Cinotti R, Duranteau J, Einav S, Ercole A, Ferguson N, Guerin C, Siempos II, Kurtz P, Juffermans NP, Mancebo J, Mascia L, McCredie V, Nin N, Oddo M, Pelosi P, Rabinstein AA, Neto AS, Seder DB, Skrifvars MB, Suarez JI, Taccone FS, van der Jagt M, Citerio G, Stevens RD (2020) Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. Intensive Care Med 46:2397–2410
10. Robba C, Battaglini D, Abbas A, Sarrió E, Cinotti R, Asehnoune K, Taccone FS, Rocco PR, Schultz MJ, Citerio G, Stevens RD, Badenes R (2024) Clinical practice and effect of carbon dioxide on outcomes in mechanically ventilated acute brain-injured patients: a secondary analysis of the ENIO study. Intensive Care Med 50:234–246
11. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF (1991) Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 75:731–739
12. Citerio G, Robba C, Rebora P, Petrosino M, Rossi E, Malgeri L, Stocchetti N, Galimberti S, Menon DK, Åkerlund C, Amrein K, Andelic N, Andreassen L, Anke A, Antoni A, Audibert G, Azouvi P, Azzolini ML, Bartels R, Barzó P, Beauvais R, Beer R, Bellander B-M, Belli A, Benali H, Berardino M, Beretta L, Blaabjerg M, Bragge P, Brazinova A, Brinck V, Brooker J, Brorsson C, Buki A, Bullinger M, Cabeleira M, Caccioppola A, Calappi E, Calvi MR, Cameron P, Carbayo Lozano G, Carbonara M, Cavallo S, Chevallard G, Chieregato A, Citerio G, Clusmann H, Coburn M, Coles J, Cooper JD, Correia M, Čović A, Curry N, Czeiter E, Czosnyka M, Dahyot-Fizelier C, Dark P, Dawes H, De Keyser V, Degos V, Della Corte F, den Boogert H, Depreitere B, Đilvesi Đ, Dixit A, Donoghue E, Dreier J, Dulière G-L, Ercole A, Esser P, Ezer E, Fabricius M, Feigin VL, Foks K, Frisvold S, Furmanov A, Gagliardo P, Galanaud D, Gantner D, Gao G, George P, Ghuysen A, Giga L, Glocker B, Golubovic J, Gomez PA, Gratz J, Gravesteijn B, Grossi F, Gruen RL, Gupta D, Haagsma JA, Haitsma I, Helbok R, Helseth E, Horton L, Huijben J, Hutchinson PJ, Jacobs B, Jankowski S, Jarrett M, Jiang J-y, Johnson F, Jones K, Karan M, G. Kolias A, Kompanje E, Kondziella D, Kornaropoulos E, Koskinen L-O, Kovács N, Kowark A, Lagares A, Lanyon L, Laureys S, Lecky F, Ledoux D, Lefering R, Legrand V, Lejeune A, Levi L, Lightfoot R, Lingsma H, Maas AIR, Castaño-León AM, Maegele M, Majdan M, Manara A, Manley G, Martino C, Maréchal H, Mattern J, McMahon C, Melegh B, Menon D, Menovsky T, Mikolic A, Misset B, Muraleedharan V, Murray L, Negru A, Nelson D, Newcombe V, Nieboer D, Nyirádi J, Olubukola O, Oresic M, Ortolano F, Palotie A, Parizel PM, Payen J-F, Perera N, Perlbarg V, Persona P, Peul W, Piippo-Karjalainen A, Pirinen M, Pisica D, Ples H, Polinder S, Pomposo I, Posti JP, Puybasset L, Radoi A, Ragauskas A, Raj R, Rambadagalla M, Helmrich IR, Rhodes J, Richardson S, Richter S, Ripatti S, Rocka S, Roe C, Roise O, Rosand J, Rosenfeld JV, Rosenlund C, Rosenthal G, Rossaint R, Rossi S, Martin Rusnák DR, Sahuquillo J, Sakowitz O, Sanchez-Porras R, Sandor J, Schäfer N, Schmidt S, Schoechl H, Schoonman G, Schou RF, Schwendenwein E, Sewalt C, Skandsen T, Smielewski P, Sorinola A, Stamatakis E, Stanworth S, Stevens R, Stewart W, Steyerberg EW, Stocchetti N, Sundström N, Takala R, Tamás V, Tamosuitis T, Taylor MS, Te Ao B, Tenovuo O, Theadom A, Thomas M, Tibboel D, Timmers M, Tolias C, Trapani T, Maria Tudora C, Unterberg A, Vajkoczy P, Vallance S, Valeinis E, Vámos Z, van der Jagt M, Van der Steen G, Naalt Jvan d, van Dijck JTJM, van Essen TA, Van Hecke W, van Heugten C, Van Praag D, van Veen E, Vyvere TV, van Wijk RPJ, Vargiolu A, Vega E, Velt K, Verheyden J, Vespa PM, Vik A, Vilcinis R, Volovici V, von Steinbüchel N, Voormolen D, Vulekovic P, K.W. Wang KKW, Wiegers E, Williams G, Wilson L, Winzeck S, Wolf S, Yang Z, Ylén P, Younsi A, Zeiler FA, Zelinkova V, Ziverte A, Zoerle T, on behalf of the Center TBIp, investigators, (2021) Management of arterial partial pressure of carbon dioxide in the first week after traumatic brain injury: results from the CENTER-TBI study. Intensive Care Medicine 47: 961-973
13. Taran S, Cho SM, Stevens RD (2022) Mechanical ventilation in patients with traumatic brain injury: is it so different? Neurocrit Care. https://doi.org/10.1007/s12028-022-01593-1
14. Harrington T, Di Chiro G (1973) Effect of hypocarbia and hypercarbia in experimental brain infarction. A microangiographic study in the monkey. Neurology 23:294–299
15. Westermaier T, Stetter C, Kunze E, Willner N, Holzmeier J, Kilgenstein C, Lee JY, Ernestus RI, Roewer N, Muellenbach RM (2014) Controlled transient hypercapnia: a novel approach for the treatment of delayed cerebral ischemia after subarachnoid hemorrhage? J Neurosurg 121:1056–1062
16. Hirsch KG, Abella BS, Amorim E, Bader MK, Barletta JF, Berg K, Callaway CW, Friberg H, Gilmore EJ, Greer DM, Kern KB, Livesay S, May TL, Neumar RW, Nolan JP, Oddo M, Peberdy MA, Poloyac SM, Seder D, Taccone FS, Uzendu A, Walsh B, Zimmerman JL, Geocadin RG (2024) Critical care management of patients after cardiac arrest: a scientific statement from the American Heart Association and Neurocritical Care Society. Neurocrit Care 40:1–37
17. Eastwood G, Nichol AD, Hodgson C, Parke RL, McGuinness S, Nielsen N, Bernard S, Skrifvars MB, Stub D, Taccone FS, Archer J, Kutsogiannis D, Dankiewicz J, Lilja G, Cronberg T, Kirkegaard H, Capellier G, Landoni G, Horn J, Olasveengen T, Arabi Y, Chia YW, Markota A, Hænggi M, Wise MP, Grejs AM, Christensen S, Munk-Andersen H, Granfeldt A, Andersen G, Qvigstad E, Flaa A, Thomas M, Sweet K, Bewley J, Bäcklund M, Tiainen M, Iten M, Levis A, Peck L, Walsham J, Deane A, Ghosh A, Annoni F, Chen Y, Knight D, Lesona E, Tlayjeh H, Svenšek F, McGuigan PJ, Cole J, Pogson D, Hilty MP, Düring JP, Bailey MJ, Paul E, Ady B, Ainscough K, Hunt A, Monahan S, Trapani T, Fahey C, Bellomo R (2023) Mild hypercapnia or normocapnia after out-of-hospital cardiac arrest. N Engl J Med 389:45–57